ENALAPRIL MALEATE AND HYDROCHLOROTHIAZIDE - enalapril maleate and hydrochlorothiazide tablet
Taro Pharmaceuticals U.S.A., Inc.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, enalapril maleate/hydrochlorothiazide tablets should be discontinued as soon as possible. See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Rx only

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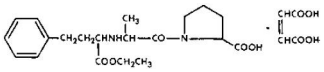
DESCRIPTION

Enalapril Maleate/Hydrochlorothiazide combines an angiotensin converting enzyme inhibitor, enalapril maleate, and a diuretic, hydrochlorothiazide.

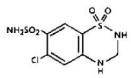
Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (*Z*)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \bullet C_4H_4O_4$, and its structural formula is:



Enalapril maleate is a white to off-white crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water but freely soluble in sodium hydroxide solution.

Enalapril maleate/hydrochlorothiazide is available in two tablet combinations of enalapril maleate with hydrochlorothiazide: enalapril maleate/hydrochlorothiazide 5/12.5, containing 5 mg enalapril maleate and 12.5 mg hydrochlorothiazide and enalapril maleate/ hydrochlorothiazide 10/25, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide. Inactive ingredients are: lactose, corn starch, sodium bicarbonate, pregelatinized starch, magnesium stearate and iron oxide.

CLINICAL PHARMACOLOGY

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of enalapril maleate blocks the renin-angiotensin-aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

In clinical studies, the extent of blood pressure reduction seen with the combination of enalapril maleate and hydrochlorothiazide was approximately additive. The antihypertensive effect of enalapril maleate/hydrochlorothiazide was usually sustained for at least 24 hours.

Concomitant administration of enalapril maleate and hydrochlorothiazide has little, or no effect on the bioavailability of either drug. The combination tablet is bio-equivalent to concomitant administration of the separate entities.

Enalapril Maleate

Mechanism of Action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril maleate alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate plus a thiazide diuretic,

there was essentially no change in serum potassium. (See **PRECAUTIONS**.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalapril remains to be elucidated.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension. Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril maleate monotherapy than non-black patients. In contrast, hydrochlorothiazide was more effective in black patients than enalapril. Concomitant administration of enalapril maleate and hydrochlorothiazide was equally effective in black and non-black patients.

Pharmacokinetics and Metabolism
Following oral administration of enalapril maleate, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60 percent. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of enalaprilat and enalapril is primarily renal. Approximately 94 percent of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40 percent of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min or less. With glomerular filtration rate ≤ 30 mL/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency. Enalaprilat is dialyzable at the rate of 62 mL/min.

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

Pharmacodynamics
Administration of enalapril maleate to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is infrequent with enalapril alone but it can be anticipated in volume-depleted patients, such as patients treated with diuretics. In clinical trials with enalapril and hydrochlorothiazide administered concurrently, syncope occurred in 1.3 percent of patients. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.)

In most patients studied, after oral administration of a single dose of enalapril maleate, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours.

At recommended doses, antihypertensive effects of enalapril maleate monotherapy have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval; this was less frequently observed with concomitant administration of enalapril maleate and hydrochlorothiazide.

Achievement of optimal blood pressure reduction may require several weeks of enalapril therapy in some patients.

The antihypertensive effects of enalapril have continued during long term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction produced by enalapril was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate, there is an increase in renal blood flow; glomular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate. (See **PRECAUTIONS, Drug Interactions, Enalapril Maleate**.)

Hydrochlorothiazide
The mechanism of the antihypertensive affect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

INDICATIONS AND USAGE
Enalapril maleate/hydrochlorothiazide is indicated for the treatment of hypertension.
These fixed dose combinations are not indicated for initial treatment (see **DOSAGE AND ADMINISTRATION**).
In using enalapril maleate/hydrochlorothiazide, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalapril does not have a similar risk. (See **WARNINGS**.)
In considering use of enalapril maleate/hydrochlorothiazide, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See **WARNINGS, Angioedema**.)

CONTRAINDICATIONS
Enalapril maleate/hydrochlorothiazide is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

General

Enalapril Maleate

Hypotension
Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving enalapril maleate/hydrochlorothiazide. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See **PRECAUTIONS, Drug Interactions**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

In patients with severe congestive heart failure, with or with out associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic in increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Anaphylactoid and Possibly Related Reactions
Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including enalapril maleate/hydrochlorothiazide) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases enalapril maleate/

hydrochlorothiazide should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See **ADVERSE REACTIONS**.)

Intestinal Angioedema
Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also **INDICATIONS AND USAGE** and **CONTRAINDICATIONS**).

Anaphylactoid reactions during desensitization
Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis
Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hepatic Failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see **PRECAUTIONS, Drug Interactions, Enalapril Maleate** and **Hydrochlorothiazide**).

Pregnancy

Enalapril-Hydrochlorothiazide
There was no teratogenicity in mice given up to 30 mg/kg/day or in rats given up to 90 mg/kg/day of enalapril in combination with 10 mg/kg/day of hydrochlorothiazide. These doses of enalapril are 4.3 and 26 times (mice and rats, respectively) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis (mg/m^2); the dose of hydrochlorothiazide is 0.8 times (in mice) and 1.6 times (in rats) the MRHDD. At these doses, fetotoxicity expressed as a decrease in average fetal weight

occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, enalapril maleate/hydrochlorothiazide should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality,* below.)

Enalapril Maleate

Fetal/Neonatal Morbidity and Mortality
ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected ACE inhibitors should be discontinued as soon as possible.

In a published restrospective epidemiological study, infants whose mothers had taken an ACE inhibitor during their first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, a patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of enalapril maleate/ hydrochlorothiazide as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, enalapril maleate/hydrochlorothiazide should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 times and 12 times, respectively, the MRHDD.

Hydrochlorothiazide
Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses of up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus. These doses are more than 150 times the MRHDD on a body surface area basis. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

PRECAUTIONS

General

Enalapril Maleate

Aortic Stenosis/Hypertrophic Cardiomyopathy
As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reductions of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia
Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough
Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients

Angioedema
Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension
Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia
Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia
Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy
Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril maleate/hydrochlorothiazide is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Enalapril Maleate

Hypotension – Patients on Diuretic Therapy
Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See **WARNINGS**, and **DOSAGE AND ADMINISTRATION**.)

Agents Causing Renin Release
The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Non-steroidal Anti-inflammatory Agents
In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate. However, reports suggest that

NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Other Cardiovascular Agents
Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium
Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium
Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics – potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin) – dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs – additive effect or potentiation.

Cholestyramine and colestipol resins – Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH – intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) – possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) – possible increased responsiveness to the muscle relaxant.

Lithium – should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with enalapril maleate/ hydrochlorothiazide.

Non-steroidal Anti-inflammatory Drugs – In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when enalapril maleate/hydrochlorothiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.

Enalapril Maleate
There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis).

Hydrochlorothiazide
Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice at doses up to approximately 600 mg/kg/day (53 times the MRHDD when compared on a body surface area basis) or in male and female rats at doses up to approximately 100 mg/kg/day (18 times the MRHDD when compared on a body surface area basis). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. In mice and rats these doses are 9 times and 0.7 times, respectively, the MRHDD when compared on a body surface area basis.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See **WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality**.

Nursing Mothers
Enalapril, enalaprilat, and hydrochlorothiazide have been detected in human breast milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue enalapril maleate/hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies of enalapril maleate/hydrochlorothiazide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS
Enalapril maleate/hydrochlorothiazide has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with enalapril maleate/hydrochlorothiazide no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.
The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Generally, adverse experiences were mild and transient in nature. Adverse experiences occurring in greater than two percent of patients treated with enalapril maleate/hydrochlorothiazide in controlled clinical trials are shown below.
Percent of Patients in Controlled Studies

	enalapril maleate/hydrochlorothiazide (n=1580) Incidence (discontinuation)	**Placebo (n=230) Incidence**
Dizziness	8.6 (0.7)	4.3
Headache	5.5 (0.4)	9.1
Fatigue	3.9 (0.8)	2.6

Cough	3.5 (0.4)	0.9
Muscle Cramps	2.7 (0.2)	0.9
Nausea	2.5 (0.4)	1.7
Asthenia	2.4 (0.3)	0.9
Orthostatic Effects	2.3 (<0.1)	0.0
Impotence	2.2 (0.5)	0.5
Diarrhea	2.1 (<0.1)	1.7

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema
Angioedema has been reported in patients receiving enalapril maleate/hydrochlorothiazide, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalapril maleate/hydrochlorothiazide should be discontinued and appropriate therapy instituted immediately. (See **WARNINGS**.)

Hypotension
In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See **WARNINGS**.)

Cough
See **PRECAUTIONS, Cough**.

Clinical Laboratory Test Findings

Serum Electrolytes
See **PRECAUTIONS**.

Creatinine, Blood Urea Nitrogen
In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with enalapril maleate/hydrochlorothiazide. More marked increases have been reported in other enalapril exper-ience. Increases are more likely to occur in patients with renal artery stenosis. (See **PRECAUTIONS**.)

Serum Uric Acid, Glucose, Magnesium, and Calcium
See **PRECAUTIONS**.

Hemoglobin and Hematocrit
Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalapril maleate/hydrochloro-thiazide but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests
Rarely, elevations of liver enzymes and/or serum bilirubin have occurred (see **WARNINGS, Hepatic Failure**).

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate
Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also see with enalapril maleate/hydrochlorothiazide. However, since enalapril has been marketed, the following adverse reactions have been reported: B*ody As A Whole:* Anaphylactoid reactions (see **WARNINGS, Anaphylactoid reactions during membrane exposure***); Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see **WARNINGS, Hypotension**); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris, Raynaud's phenomenon; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice) (see **WARNINGS, Hepatic Failure**), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia,

thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia), dream abnormality; *Urogenital:* Renal failure, oliguria, renal dysfunction, (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, eosinophilic pneumonitis, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous
A symptom complex has been reported which may include some or all of the following: a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality
See **WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality**.

Hydrochlorothiazide
Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskelatal:* Muscle spasm; *Nervous System/ Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see **WARNINGS**); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

OVERDOSAGE
No specific information is available on the treatment of overdosage with enalapril maleate/hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with enalapril maleate/hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include the induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalapril Maleate
Single oral doses of enalapril above 1,000 mg/kg and ≥ 1,775 mg/kg were associated with lethality in mice and rats, respectively. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis. (See **WARNINGS, Anaphylactoid Reactions During Membrane Exposure**.)

Hydrochlorothiazide
Lethality was not observed after administration of an oral dose of 10 g/kg to mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

DOSAGE AND ADMINISTRATION
Enalapril and hydrochlorothiazide are effective treatments for hypertension. The usual dosage range of enalapril is 10 to 40 mg per day administered in a single or two divided doses; hydrochlorothiazide is effective in doses of 12.5 to 50 mg daily. The side effects (see **WARNINGS**) of enalapril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of enalapril and hydrochlorothiazide will be associated with both sets of dose-independent side effects but the addition of enalapril in clinical trials blunted the hypokalemia normally seen with diuretics. To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

Dose Titration Guided by Clinical Effect
A patient whose blood pressure is not adequately controlled with either enalapril or hydrochlorothiazide monotherapy may be given enalapril maleate/hydrochlorothiazide 5/12.5 or enalapril maleate/hydrochlorothiazide 10/25. Further increases of enalapril, hydrochlorothiazide or both depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. In general, patients do not require doses in excess of 20 mg of enalapril or 50 mg of hydrochlorothiazide. The daily dosage should not exceed four tablets of enalapril maleate/hydrochlorothiazide 5/12.5 or two tablets of enalapril maleate/ hydrochlorothiazide 10/25.

Replacement Therapy
The combination may be substituted for the titrated components.

Use in Renal Impairment
The usual regimens of therapy with enalapril maleate/hydrochlorothiazide need not be adjusted as long as the patient's creatinine clearance is >30 mL/min/1.73m^2 (serum creatinine approximately ≤3 mg/dL or 265 µmol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so enalapril maleate-hydrochlorothiazide is not recommended (see **WARNINGS, Anaphylactoid reactions during membrane exposure**).

HOW SUPPLIED
Enalapril Maleate and Hydrochlorothiazide Tablets USP, 5/12.5 mg, are ivory, caplet-shaped compressed tablets, engraved on one side with T4. Each tablet contains 5 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide. They are supplied as follows:
NDC 51672-4045-1 bottles of 100 (with desiccant).
NDC 51672-4045-3 bottles of 1,000 (with desiccant).
Enalapril Maleate and Hydrochlorothiazide Tablets USP, 10/25 mg, are peach, caplet-shaped, compressed tablets, engraved on one side with T3. Each tablet contains 10 mg of enalapril maleate and 25 mg of hydrochlorothiazide. They are supplied as follows:
NDC 51672-4046-1 bottles of 100 (with desiccant).
NDC 51672-4046-3 bottles of 1,000 (with desiccant).

Storage
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture.
Dispense in a tight container as per USP, if product package is subdivided.
Mfd. By:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. By:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
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